

Functional repertoire of protein kinases and phosphatases in synaptic plasticity and associated neurological disorders

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Raheel Khan^{1,2}, Don Kulasiri^{1,2,*}, Sandhya Samarasinghe¹

Abstract

Protein phosphorylation and dephosphorylation are two essential and vital cellular mechanisms that regulate many receptors and enzymes through kinases and phosphatases. Ca^{2+} -dependent kinases and phosphatases are responsible for controlling neuronal processing; balance is achieved through opposition. During molecular mechanisms of learning and memory, kinases generally modulate positively while phosphatases modulate negatively. This review outlines some of the critical physiological and structural aspects of kinases and phosphatases involved in maintaining postsynaptic structural plasticity. It also explores the link between neuronal disorders and the deregulation of phosphatases and kinases.

Key Words: Alzheimer's disease; autism spectrum disorder; CaMKII; calcineurin; long-term depression; long-term potentiation; protein kinase A; protein phosphatase 1; protein dephosphorylation; protein phosphorylation

Introduction

Our nervous system has an extraordinary capacity to adapt, form, and store memories based on activity-dependent synaptic alterations. It is well-known that synaptic functions are correlated with structural changes in the synapse (Matsuzaki et al., 2004; Bonhoeffer and Caroni, 2016). However, the interrelationship between functional and structural changes is poorly understood in terms of memory formation and stabilization (Meyer et al., 2014; Monday and Castillo, 2017). Experimental studies have identified the biochemical basis for synaptic plasticity, that is, long-term potentiation (LTP) (an activity-dependent increase in synaptic efficacy), and long-term depression (LTD) (an activity-dependent decrease in synaptic efficacy) (Malenka and Bear, 2004). However, structural changes related to memory have not been explained in sufficient detail (Sala and Segal, 2014; Holtmaat and Caroni, 2016).

Lisman proposes a bi-stable system consisting of two major classes of biomolecules; that is, protein kinases (PKs) which are capable of phosphorylation and protein phosphatases (PPs) which can dephosphorylate PKs (Lisman et al., 1985). These mechanisms are considered bi-stable elements of synaptic plasticity. A kinase-phosphatase system can be triggered by an external stimulus, and it remains active despite protein turnover (Zhabotinsky, 2000; Pi and Lisman, 2008). Therefore, the specific outcome of synaptic plasticity is dependent upon the relative balance between PPs and PKs coordinated activity (Pagani and Merlo, 2019). Numerous studies on learning and memory have been reported the coordinated activity relationship between PKs and PPs (Woolfrey and Dell'Acqua, 2015). In a neuron, key PPs and PKs work in opposition to maintain balance (Hu et al., 2003). For example, PKs activity

increases during LTP and decreases during LTD. However, in the case of PPs, activity decreases during LTP and increases during LTD (Pi and Lisman, 2008; Pagani and Merlo, 2019). These activities involve both structural and functional changes in the nervous system (Thiels et al., 1998; Rozov et al., 2017). An overall increase in postsynaptic size and volume has been reported during LTP (Petrovic et al., 2017; McLeod et al., 2018). In contrast, studies on LTD have shown a postsynaptic decrease in size and volume (Becker et al., 2008; Sala and Segal, 2014). These changes are dependent on the behaviour of both PKs and PPs, involved in the regulatory mechanisms of synaptic plasticity (Shi, 2009; Sanderson et al., 2018). Any disturbance in the balance or activity impairs the memory and learning process that can lead to neuropathological conditions. Therefore, it is necessary to discuss here key PKs and PPs at the molecular level to understand the structural and functional memory-related abnormalities.

In this review, we explain the critical PKs and PPs involved in the memory process. It includes essential PKs involving Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) (McDonald and Moss, 1994; Blitzer et al., 1998), cAMP-dependent protein kinase A (PKA) (Swope et al., 1992; Esteban et al., 2003), Ca^{2+} /phospholipid-dependent protein kinase C (PKC) (Ben-Ari et al., 1992), myosin kinase (MK) (Rex et al., 2010), Rho kinases (Lamprecht and LeDoux, 2004; Tolia et al., 2011), p21 activated kinases (PAK) (Albin and Davis, 2004; Asrar et al., 2009). We also include PPs such as Calcineurin (CN) (Rusnak and Mertz, 2000; Ke and Huai, 2003), protein phosphatase 1 (PP1) (Bollen et al., 2000; Cohen, 2002), and protein phosphatase 2A (PP2A) (Janssens and Goris, 2001).

Firstly, we discuss the physiological basis of activity-dependent synaptic changes explaining the role of PKs and PPs in LTP and

¹Centre for Advanced Computational Solutions (C-fACS), Lincoln University, Christchurch, New Zealand; ²Department of Molecular Biosciences, Lincoln University, Christchurch, New Zealand

*Correspondence to: Don Kulasiri, PhD, Don.Kulasiri@lincoln.ac.nz.

<https://orcid.org/0000-0001-8744-1578> (Don Kulasiri)

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LTD, respectively. We further discuss their regulation, based on the structural features of critical biomolecules, and highlight their effect during neuronal stimulation. Finally, we discuss the studies on neurological disorders/neuropathological conditions and their relationship with the disturbance in activity-dependent morphology of the synapse.

Search Strategy and Selection Criteria

Data retrieval

In this work, we used bibliometric methods to investigate research trends in key protein kinases and phosphatases. Lincoln University database, a research database of publications and citations created by the Lincoln University, Lincoln, New Zealand, was selected and evaluated, using the keywords 'morphological changes*', 'protein kinase*', 'protein phosphatase*', and 'neurological disorders*'. We limited the period of publication from 1990 to 2020 to evaluate the extensive research data and results.

Inclusion criteria

(a) Published and indexed peer-reviewed articles on protein kinases and phosphatases and their impact on morphology of the brain; (b) type of article: original research articles and reviews; (c) year of publication: 1970–2020.

Exclusion criteria

(a) Articles that required manual searching or telephone access; (b) a number of corrected papers or book chapters from the total number of articles.

Role of Protein Kinases and Protein Phosphatases in Long-Term Potentiation and Long-Term Depression

LTP and LTD are associated with an increase in Ca^{2+} concentration at postsynaptic sites in the hippocampal CA1 region (Wang et al., 2019). A high-frequency stimulation (HFS) cause an increase in Ca^{2+} concentration activating Ca^{2+} -sensitive PKs which are involved in LTP induction through the activation of both NMDA-glutamate receptors (NMDARs) and AMPA receptors (AMPA) (Park et al., 2016). However, a low-frequency stimulation (LFS) cause reduced Ca^{2+} influx through NMDAR resulting LTD.

NMDARs and AMPARs play a crucial role during expression of both LTP and LTD. NMDARs have a heterotetrameric structure which consists of two GluN2A-2D and two GluN1 subunits which are permeable to Ca^{2+} , Na^+ , and K^+ . NMDARs have become a significant research interest due to their involvement in multiple neurological disorders. It occurs as different subtypes with distinct composition and biophysical properties. AMPARs are also heterotetrameric structures which consist of GluA1-GluA2 subunits. In contrast, these subunits permit Na^+ and K^+ to enter the neuron and block Ca^{2+} due to its GluA2 subunits (Chater and Goda, 2014). AMPARs, with GluA1 subunits, are permeable to Ca^{2+} and present in extrasynaptic and intracellular locations (Woolfrey and Dell'Acqua, 2015).

Brief but strong Ca^{2+} influx through NMDARs can activate PKs and alter synaptic strength by modifying, adding, or removing AMPARs (Lussier et al., 2015). For example, kinases like CaMKII can enhance AMPARs activity through phosphorylating AMPARs during LTP (Huganir and Nicoll, 2013). AMPARs get phosphorylated on C-terminal residues of GluA1 subunits and thus can modify synaptic localization and channel biophysical properties (Figure 1A). This process increases synaptic incorporation and single-channel conductance during LTP. Similarly, cAMP-dependent PKA also phosphorylates AMPAR-GluA1 at Ser-845. This not only increases the probability of an open channel but also stimulates AMPARs exocytosis to

drive AMPARs for synaptic insertion during LTP (Serwach and Gruszczynska-Biegala, 2019). Consequently, although CaMKII is an essential kinase and a sensor for Ca^{2+} signalling during LTP, potentiation requires the coordinated and organised activity of multiple kinases (Figure 1B).

In LTD, phosphatases play a more significant role than kinases. LTD expression requires changes in postsynaptic NMDAR mediated Ca^{2+} influx, and activation of PP1 and/or PP2A. As a result, AMPARs dephosphorylation and subsequent changes of postsynaptic targets occur during LTD. Dephosphorylation of AMPAR-GluA1 at Ser-845 is critical to prevent recycling and a preference for receptor degradation, which causes AMPARs removal during LTD and leads to endocytosis (Anggono and Huganir, 2012; Cahill and Milton, 2019).

Studies have identified a link between PP1/PP2A activity with LTD (Chiu et al., 2019). Similarly, CN is the primary and direct transducer of NMDAR Ca^{2+} signalling during LTD, but other PPs and PKs also play critical roles during LTD (Figure 1C).

Regulation of Postsynaptic Protein Kinases and Structural Plasticity

Ca^{2+} /CaMKII

CaMKII is a multifunctional kinase classified as a Serine/Threonine kinase. It controls various Ca^{2+} mediated activities within neurons, including synaptic plasticity, gene expression, and neurotransmitter release (Skelding and Rostas, 2020). It can be divided into 12-meric holoenzyme from α , β , γ , and δ isoforms (Figure 2A). α isoforms are found in excess in neurons, compared to β , γ , and δ . CaMKII is involved in Ca^{2+} regulation and mainly enriched at synapses (Myers et al., 2017). During its activation state, there is a time window in which actin can be significantly reorganized (Incontro et al., 2018). In this way, CaMKII assumes a bifunctional role in synaptic plasticity: a structural role during the basal state, linking structural and functional plasticity, and a signalling role in transient periods of neuronal activity (Herring and Nicoll, 2016).

HFS causes Ca^{2+} elevation in the postsynaptic neuron (Dittmer et al., 2019) to form a Calcium-Calmodulin (Ca^{2+} – CaM) complex. Ca^{2+} – CaM binds with CaMKII, exposing the active site (Thr-286 in the case of CaMKII- α , Thr-287 in the case of β , γ , δ) in exogenous substrates and autoinhibitory domain (Bhattacharyya et al., 2016, 2020). In the case of CaMKII- α , Thr-286 is involved in autophosphorylation, which plays a critical role in the functional modification of CaMKII. Functional modification occurs in two ways. Firstly, the saturation of CaMKII with Ca^{2+} increases Ca^{2+} – CaM binding affinity. Secondly, it prevents the active site of the autoinhibitory domain from taking over to keep kinase partially active. This practice is described as CaMKII autonomy (Figure 2B) (Woolfrey and Dell'Acqua, 2015).

CaMKII plays a significant role in AMPARs trafficking. Phosphorylation of the AMPAR-GluA1 subunit at Ser 831 promotes AMPARs trafficking (Diering and Huganir, 2018; Jurado, 2018). HFS causes the rapid phosphorylation of AMPARs, GTPase regulators, and adhesion molecules (Araki et al., 2015). Several Transmembrane AMPAR Regulatory Proteins (TARPs) have been identified that control both trafficking and functional properties of AMPARs (Coombs and Cull-Candy, 2009; Park, 2018). Stargazin is one of the critical TARP that regulates AMPARs recruitment by PSD-93 and PSD-95 and trafficking within synapse (Elias et al., 2008; Vallejo et al., 2017). Ca^{2+} entry, through NMDAR, encourages the phosphorylation of stargazin by decreasing stargazin C terminus association with the plasma membrane, thus rendering it closer to CaMKII. The consequent phosphorylation promotes stargazin C terminus binding with PSD-95, thus

preventing re-association with the plasma membrane (Hell, 2014).

The structural plasticity of dendritic spines requires CaMKII activity. Pharmacological inhibitory studies, which use NMDAR and CaMKII inhibitors to prevent glutamate-induced long-term enlargement, suggest activity-dependent spine growth. While the kinase activity of CaMKII is not involved in the maintenance and stabilization of the spinal structure (Borovac et al., 2018), it is essential for structural plasticity (Okamoto et al., 2004). CaMKII activation triggers several signalling pathways through Rho-GTPases activation that modulate equilibrium between G-actin and F-actin. However, as CaMKII is abundant in the spine, the core target of CaMKII kinase activity may be CaMKII itself. One subunit of activation leads to the rapid phosphorylation of the other subunits. This process enables CaMKII to bind directly to F-actin (Okamoto et al., 2009; Borovac et al., 2018) and regulates actin filament bundling through the β -subunit in basal conditions, thereby preserving the stability of the spinal structure (**Figure 3**).

cAMP-dependent protein kinase A

PKA is another critical kinase involved directly or indirectly in several signalling processes in the CNS. It has several downstream targets. PKA activation is dependent on cAMP concentration and, therefore, termed as a cAMP-dependent protein kinase. PKA has a heterotetrameric structure; it consists of two catalytic and two regulatory subunits. It combines with other proteins, especially with A-kinase anchoring proteins (AKAPs), which further regulates its activity (Taylor et al., 2012). The presence of cAMP is necessary for PKA activation. In the absence of cAMP, the catalytic domain remains hidden, thereby preventing PKA kinase activity. cAMP binding to the regulatory domain causes the proteins to dissociate, exposing the catalytic subunits, which triggers PKA kinase activity (Pittenger et al., 2012).

The mammalian PKA consists of three Catalytic (C) and four regulatory (R) subunits: C α , C β , C γ and R1 α , R1 β , R1 α , R1 β (Abel and Nguyen, 2008). Each subunit is encoded by a typical gene (Døskeland et al., 1993). PKA isozymes (types I and II) were initially identified and characterized on the basis of their patterns, using the chromatographic technique (Nguyen and Woo, 2003). In the absence of cAMP, PKA remains inactive and exists in a tetrameric holoenzyme with two R subunits bound to two C subunits (**Figure 4**). Each regulatory subunit can be divided into two cAMP binding sites: a low-affinity site followed by a high-affinity site (Taylor et al., 1990; Ohta et al., 2018). Cooperative and sequential cAMP binding on the R subunits results in dissociation of the monomeric C subunits (Woo et al., 2002). These released C subunits phosphorylate Serine and Threonine residues on several proteins. Essentially, the regulatory subunits act like pseudosubstrate inhibitors which hinder phosphotransferase activities of the catalytic subunits (Garetto, 2018).

NMDAR-mGluR, and dopamine receptor signalling cause adenylate cyclase (AC) to synthesize cAMP in dendritic spines (Borovac et al., 2018). Strong synaptic stimulation causes an influx of Ca²⁺ into the postsynaptic neuron. This leads to CaMKII activation and the activation of the cAMP/PKA pathway at the same time. As PKA inhibits PP1, which inactivates CaMKII by dephosphorylation, a prolonged cAMP presence in the spine may extend the activation time of CaMKII during synaptic plasticity (**Figure 4**) (Blitzer et al., 1998).

The cAMP pathway plays an important role in the later phase of LTP (L-LTP), which requires gene expression and local protein synthesis (Kandel, 2012). Postsynaptic cAMP causes cAMP Responsive Element Binding (CREB) transcription factor activation and enhances specific transcript activity during L-LTP (Borovac et al., 2018). Frey et al. (1993) suggest that an increase in cAMP activity may lead to L-LTP. Scientists have also

studied the role of cAMP during the early phase of LTP (E-LTP), in relation to structural changes in the spine. Results confirm the involvement of cAMP in the enhancement of structural potentiation, postsynaptically. This process results in strong structural potentiation of the spine (Borovac et al., 2018), possibly by extending the time window for actin cytoskeleton remodelling. Similarly, a pharmacological study confirms the involvement of cAMP in the structural enlargement of spines (Govindarajan et al., 2011).

Ca²⁺/phospholipid-dependent protein kinase C

The identification of PKA also led to the discovery of the signal transduction pathway (Dekker, 2004). Likewise, structural plasticity is dependent on intercellular signalling networks. In the mid and late 1970s, Nishizuka et al. reported the presence of a cyclic nucleotide-independent kinase (PKC) which could be activated by a combination of Ca²⁺, phospholipids, and diacylglycerol (Nishizuka, 1984). PKC exists in almost nine isoforms; α , β and γ were the first isoforms to be identified. Low stringency screening, a molecular biology technique, led to the identification of three more isoforms: PKC- δ and ϵ , ζ . Subsequently, PKC- η , θ and ι isoforms are identified through the screening of non-libraries (Kofler et al., 2002).

The intercellular signal transduction pathway depends on the ability of receptors, present on the cell surface, to stimulate phospholipase C. Subsequently, phospholipase C stimulates phosphatidylinositol 4,5-bisphosphate (PIP3) which triggers phosphoinositide-dependent kinase (PDK) to phosphorylate PKC and other kinases (Pham and Tonetti, 2018). In cultured hippocampal neurons, PKC activation produces rapid and novel lamellae formation over a large surface of dendrites. This involves PKC activation at postsynaptic sites; this involves actin polymerization but not Erk activation. PKC regulates Rac1 and RhoA (upon activation), to produce structural plasticity in spines and dendrites (Pilpel and Segal, 2004). Likewise, PKC inhibition hinders both transient and sustained phases of structural plasticity (Murakoshi et al., 2017).

Memory-specific PKC translocation from cytosol to membrane, in dendritic regions of the mammalian hippocampus, confirms PKC-regulated structural changes or increases in spine sizes (Antunes et al., 2016). Memory-specific enhancement of synaptic potentials in the CA1 pyramidal cells has also been reported upon exogenous activation of PKC (Frick et al., 2018). Essentially, PKC signalling pathways control dendritic morphology in cultured neuronal synaptic preparation and juvenile brain slices (Hongpaisan and Alkon, 2007).

Myosin kinases

Myosin kinase plays a major role in morphological changes of the spine during synaptic plasticity. Myosin I and II, present in almost all eukaryotic cells, are the most abundant proteins and thus, have been widely studied. A typical myosin molecule consists of one or two heavy chains and several light chains. The heavy chains are arranged into three distinct domains, both functional and structural: the head, the neck and the tail domain (Woodhead and Craig, 2020). The head domain is responsible for generating force and contains ATP and actin-binding sites. The α -helical neck domain lies next to the head domain, which is connected to the light chains and controls the activity of the head domain. The third and last domain, the tail domain, consists of the binding regions that regulate the specific functions of a particular myosin (**Figure 5**) (Lodish et al., 2000).

The non-muscle myosin IIb (isoform) has fascinating properties. It is considered an actin-binding motor protein due to its mechanochemical activity. Acting as a motor, myosin moves along the actin filaments. It uses ATP as an energy source (Lodish et al., 2000; Walklate et al., 2016). Non-muscle myosin IIb primarily gets phosphorylated at Ser19 of the regulatory light chain which results in binding the NMDAR

(C-termini of NR1 and NR2) with the regulatory light chain (Amparan et al., 2005). Signalling pathways, specifically in the PSD, control the phosphorylation state of the myosin light chain. It has been reported that the P21-associated kinase (PAK) and the Rho-associated kinase (ROCK) modulate spine morphology and phosphorylate myosin IIb directly. Myosin kinase plays a key role in stimulus-induced F-actin reorganization, particularly in the regulation of dynamic cellular structures (Cole and Walsh, 2017). It can contract and bind reversibly with actin. Spine motility and morphology are modulated by actin polymerization and depolymerization. As it can be regulated bidirectionally during synaptic plasticity, myosin appears to be a potent and novel regulating switch that controls the dynamic structure of dendritic spines (Elezz et al., 2016).

Rho kinases (Rac, RhoA, and Cdc42), and p21 activated kinases

Synaptic plasticity and spine morphogenesis depend on the dynamic remodelling of actin cytoskeleton within spines (Amparan et al., 2005). Actin reorganization is modulated by Rho-like GTPases, including RhoA, Rac, and Cdc42. These act like molecular switches that regulate spine and dendritic morphology; that is, structural plasticity (Newey et al., 2005; Martin-Vilchez et al., 2017). Active Cdc42 and Rac1 regulate spine enlargement, formation, and maintenance. In contrast, RhoA decreases spine stability and density (Newey et al., 2005; Ju and Zhou, 2018). Studies on mental retardation have shown the close relationship between human cognitive development and the Rho GTPase pathway, with the identification of several proteins in this pathway. This evidence proves that anatomical alteration is linked with altered spine morphology (van Galen and Ramakers, 2005). While Guanine-nucleotide exchange factors (GEFs) activate RhoGTPases, it is deactivated by GTPase (GAPs) activating proteins. Notably, several GAPs and Rho GEFs that are positioned in dendritic spines perform an important role in morphogenesis of the dendritic spine (Fu and Ip, 2017).

The p21 activated kinases (PAKs) are important effector proteins for the Rho GTPases, Rac and Cdc42. The PAKs are classified into a family of six members, which are further divided into two families of proteins. They are identified numerically. The first family consists of PAK-1, 2, and 3. PAK-4, 5 and 6 form the second family. While some of the PAKs have specific tissues, others are freely expressed. PAK is another Serine/Threonine kinase found in the nervous system. It is an effector protein in the Rho GTPase, Rac and Cdc42. PAKs regulate the cytoskeleton, modifying the cell motility, adhesion, and shape. The PAKs are involved in the formation of filopodia and lamellipodia (filamentous forms of actin) and regulate the cytoskeleton mainly through controlling F-actin. Studies have also reported their influence on microtubule organization (Kumar et al., 2017).

Regulation of Postsynaptic Protein Phosphatases and Structural Plasticity

PKs act as primary effectors of phosphorylation. In contrast, phosphatases drive dephosphorylation (Hedrick and Yasuda, 2017; Matt et al., 2019). However, both processes, protein phosphorylation and dephosphorylation, are dynamic and are balanced to ensure biochemical equilibrium between these proteins. Any subtle change in extracellular signalling causes rigorous changes in PPs activity and alterations in the phosphorylation state of the cytoskeletal proteins (Hoffman et al., 2017). In the brain, most Serine/Threonine dephosphorylation is facilitated by phosphoprotein phosphatases types 1 (PP1), 2 (PP2A) and Calcineurin (CN) (Brautigam and Shenolikar, 2018).

Protein phosphatase 1

PP1 is initially considered to be a key regulator in glycogen metabolism (Printen et al., 1997). Today, its role in the cellular processes, such as muscle contractility, cell division, translation, transcription, and apoptosis, is well-known (Munton et al., 2004). In the brain, PP1 is highly expressed in the form of its catalytic subunits. Studies on α , β , $\gamma 1$, and $\gamma 2$ isoforms indicate its importance in neural pathways (Rosso et al., 2016). The classification of these isoforms is based on their interactions with other regulatory proteins and their subcellular locations. For example, while the β isoform is highly expressed in the nerve cell body, $\gamma 1$ is found, both in the soma where it is highly expressed in presynaptic boutons and, in the dendrites where it colocalizes with several neuronal proteins like CaMKII (Munton et al., 2004).

The strengthening and weakening of synapses or synaptic plasticity are associated with bidirectional changes in neuronal excitability (Munton et al., 2004; Seibt and Frank, 2019). HFS increases synaptic efficacy which is associated with LTP. This results in transient Ca^{2+} ion entry, mediated by NMDAR, causing a constant increase in CaMKII activation due to autophosphorylation at Thr-286. However, in LTD, synaptic efficacy is reduced. This process is due to low-frequency stimulation, initiated by pathways involving PP1 and CN (Lisman et al., 2002; Henson et al., 2017). PP1 activity is tightly regulated in CaMKII signalling, which involves PKA led phosphorylation of the inhibitory PP1-interacting protein (I1). Interestingly, LTP induction results in cAMP-dependent endogenous I1 phosphorylation, which in turn causes decreased PP1 activity (Borovac et al., 2018) (**Figure 6**).

Regulatory pathways involving PP1 are principally responsible for establishing structural plasticity in long term memory. Learning induces not only molecular changes but also structural modifications (Hoffman et al., 2017). However, the reasons why, and the extent to which these changes occur, are not well-known. Interestingly, the involvement of PP1 has been identified during the motility of dendritic spines which are regulated by an interacting network of signalling pathways (Rangamani et al., 2016). These signalling pathways influence the dynamic reorganization of the actin system in spines. However, various regulatory subunits can restrict and facilitate PP1 activity; regulatory subunits are seemingly crucial for the regulation of spine motility (Munton et al., 2004).

Nurabins are the major regulatory subunits that bind PP1 catalytic subunits to dendritic spines. Notably, neurabin I and neurabin II (spinophilin), two neurons isoforms, have been identified in vertebrates with 48% amino acid sequence similarity (MacMillan et al., 1999). Neurabin I and spinophilin both have a large scaffolding structure with a series of protein-interacting domains. Studies using genetic or molecular manipulations to eliminate neurabins from cells have shown that neurabins play a vital role in determining the neural process. Knockout mice studies, lacking spinophilin, show noticeable results, including a higher number of dendritic spines with reduced brain size, reduced LTD with altered AMPA receptors and NMDAR functions, and higher resistance to kainate-induced seizures and apoptosis (Lee et al., 2000). Accordingly, it appears that neuronal development, functions, and morphology are greatly affected by not allowing PP1 to anchor to dendritic spines. However, further studies are required to establish the role of neurabins in structural plasticity (MacMillan et al., 1999). Yataio, is another protein that binds with PP1 and facilitates the dynamic regulation of an individual phosphoprotein. It forms a signalling complex between PKA and PP1 that contribute to the regulation of Ca^{2+} influx through NMDARs (Clark et al., 2011).

Protein phosphatase 2A

Protein phosphatase 2A (PP2A) is an essential enzyme in

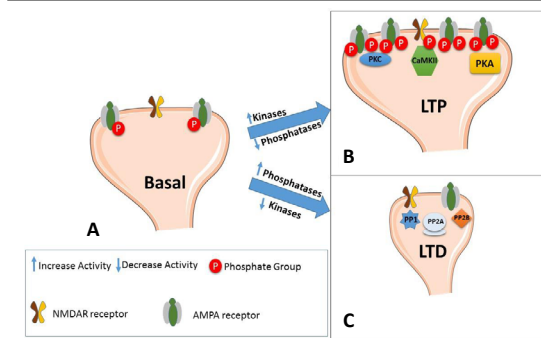


Figure 1 | Coordinated activity of protein kinases during LTP and LTD. (A) Postsynaptic neuron at the basal state before stimulation, (B) Structural plasticity of a postsynaptic neuron after high-frequency stimulation with an increase in the number of AMPARs and overall postsynaptic neuron size increases, and (C) Postsynaptic neuron after low-frequency stimulation causing dephosphorylation and shrinkage in the neuron (size). LTD: Long-term depression; LTP: long-term potentiation; NMDAR: N-methyl-D-aspartate receptor; PKA: protein kinase A.

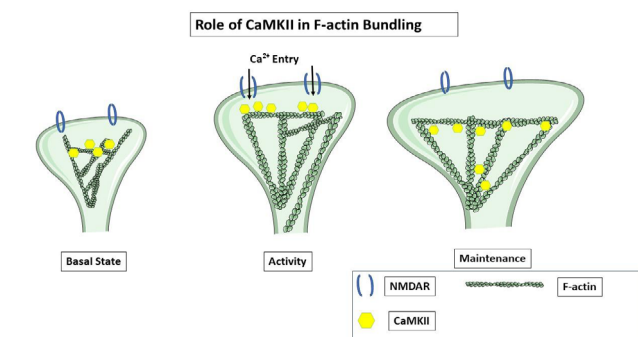


Figure 3 | Role of CaMKII in F-actin bundling. CaMKII regulation of the actin filaments bundling in the basal conditions, thereby preserving the stability of the spine structure. In the activity stage, CaMKII kinase activity initiates autophosphorylation causing its dissociation from the actin filaments. In the maintenance stage, it leads to dissociation from the actin filaments and permits successive reorganization of the dendritic spine structure. CaMK: Calmodulin-dependent protein kinase; NMDAR: N-methyl-D-aspartate receptor.

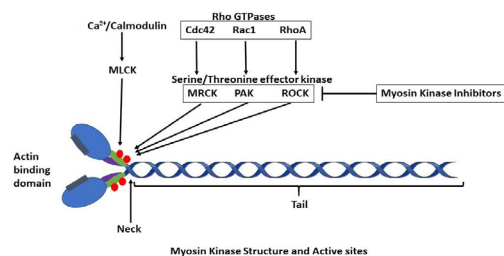


Figure 5 | Myosin kinase structure with active sites. A typical myosin molecule consists of one or two heavy chains and various light chains. The heavy chains are arranged into three distinct domains, both functional and structural. The α -helical neck domain lies next to the head domain, which is connected to the light chains. It controls the activity of the head domain. The third and last domain, the tail domain, consists of the binding regions that regulate the specific functions of a particular myosin. PAK: P21-associated kinase; ROCK: Ras homology-associated kinase.

human beings; it represents 0.3 to 1% of total cellular proteins (Ruediger et al., 1991; Lin et al., 1998). The mammalian PP2A exists as a heterotrimer with a scaffolding subunit A (PP2R1 A, PP2R1 B), a catalytic subunit C (PP2Ac) and one regulatory B-type subunit. Four distinct families have been identified, which contain one of 23 regulatory B-type subunits: that is, B (PP2R), B' (PP2R5), B'' (PP2R3) or B'''/striatins (PPP2R4). Each family consists of several isoforms. Other unclassified regulatory subunits, like $\alpha 4$, are also associated with PP2Ac.

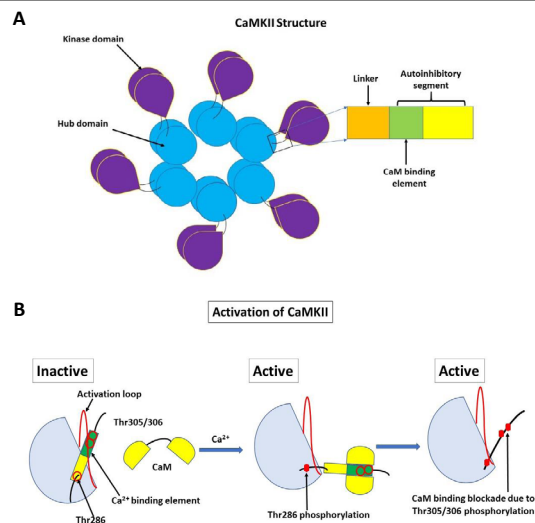


Figure 2 | CaMKII structure and function. (A) Structure of CaMKII 12-meric holoenzyme; (B) CaMKII activation by CaM. To keep the kinase partially active, it prevents the active site of the autoinhibitory domain from taking over; this process is described as CaMKII autonomy. CaMK: Calmodulin-dependent protein kinase.

PKA indirect role in spine cytoskeleton regulation

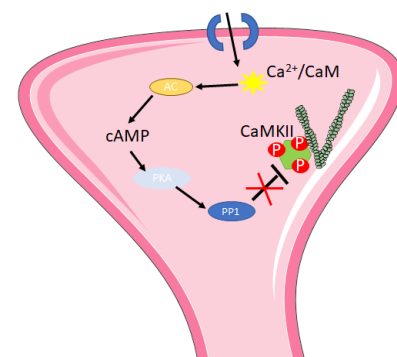


Figure 4 | PKA indirect role in spine cytoskeleton regulation. PKA inhibits PP1, which inactivates CaMKII by dephosphorylation. Prolonged cAMP presence in the spine may extend the activation time of CaMKII during synaptic plasticity. CaMK: Calmodulin-dependent protein kinase; PKA: protein kinase A; PP1: protein phosphatase 1.

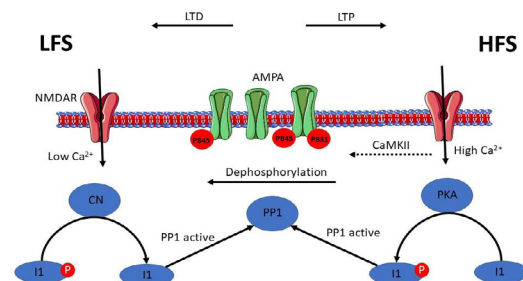


Figure 6 | PP1 regulation in CaMKII signalling. PKA led phosphorylation of the inhibitory PP1-interacting protein (I1). LTP induction results in cAMP-dependent endogenous I1 phosphorylation, causing decreased PP1 activity. CN: Calcineurin; HFS: high-frequency stimulation; LFS: low-frequency stimulation; NMDAR: N-methyl-D-aspartate receptor; PKA: protein kinase A; PP1: protein phosphatase 1.

These regulatory subunits are the most complex subunits of PP2A. They are involved in the determination of subcellular localization, stability, enzyme biogenesis, and substrate specificity (Haesen et al., 2012). For example, studies have identified structural differences in B and B' families of regulatory subunits. These differences in functions affect the binding to the scaffolding A and catalytic C subunits of PP2A (Xu et al., 2006, 2008; Cho and Xu, 2007).

Certain cellular regulators and natural inhibitors, like okadaic

acid (OA), are also involved in regulating PP2A activity (Abal et al., 2018). These inhibitors constrain not only all PP2A isoforms but also the activity of other Ser/Thr phosphatases, including PP1 and PP2 family members (Chiu et al., 2019). Presently, very little is known about phosphatase activity during and after LTP induction, due to a lack of direct biochemical data. However, the available evidence suggests that LTP induction is related to the inhibition of PP1 and PP2A and the activation of CN (Wang et al., 2019).

Alterations to PP2A could lead to apoptosis and disturbance in the cytoskeleton structure (Zhu et al., 2010). Similarly, decreased PP2A activity promotes neuronal apoptosis through both Akt phosphorylation at T308 and S473v and Bad (pro-apoptotic molecule) phosphorylation at S112 and S136. In patients with Alzheimer, neuronal loss is associated with hyperphosphorylation of tau (an essential protein), the production of A β and memory loss (Bertoli et al., 2009). Interestingly, *in vivo* studies demonstrate that the inhibition of PP2A causes hyperphosphorylation of tau and consequently, spatial memory loss. However, these effects can be reversed by the application of acetyl-L-carnitine (Martin et al., 2013).

Protein phosphatase 2B–calcineurin

Protein phosphatase 2B or calcineurin (CN) is discovered as a potential substrate for the immunosuppressants, FK506/tacrolimus and cyclosporin A; upon binding, it prevents the recruitment of macromolecules to the active site (Griffith et al., 1995). PP1 and CN share a 40% sequence similarity. Mutation studies on chimeric PP1-CN demonstrate how CN and PP1 differ in their response to inhibitory toxins, such as microcystin-LR and OA, due to PP1c's different amino acid sequence (β 12– β 33 loop) (Maynes et al., 2001).

While CN is a Ca²⁺-calmodulin-dependent enzyme found in several cell types, it is mainly expressed in the neuronal cell body and processes (Ferreira et al., 1993). Interestingly, it is the most abundant calmodulin-binding protein in the adult brain (Klee et al., 1979). CN performs a key role in the establishment of synaptic plasticity and memory (Mansuy, 2003). It consists of a catalytic and a regulatory subunit is known as an “A or CNA” subunit (PPP3C A/B/C isoforms) and “B or CNB” subunit (PPP3R 1/2 isoforms), respectively. Catalytic subunit interaction with calmodulin is dependent on Ca²⁺ influx.

In contrast, the regulatory subunit contains four Ca²⁺ binding sites. The subunits work together to regulate CN activity. CN isoforms are compartmentalized throughout cells. They interact with various anchoring proteins which determine substrate specificity (Dodge and Scott, 2003). CN regulates abundant targets concurrently in numerous cellular compartments. In addition to its substrate-specific behavior, CN can potentially interact with other PP1s. Indeed, studies have shown that PP1 inhibition in the adult brain improves learning and memory and mimics some of the effects of CN inhibition. This finding reveals that the two PP1s share the same pathways (Hoffman et al., 2017). CN recruits cellular and molecular mechanisms that can modulate plasticity and synaptic transmission, thus enhancing the brain's information processing efficacy. As a result of its ability to downregulate several pre and postsynaptic targets, CN is considered a key molecule for curtailing LTP at the molecular level. CN also participates in LTP regulation by controlling neuromodulatory systems. It modulates the activity of various G protein-coupled receptors, including metabotropic glutamate receptors (groups I and II); for example, CN directly dephosphorylates mGluR5 receptors. This practice prevents PKC from making structural modifications (Alagarsamy et al., 2005; Hoffman et al., 2017).

Activity-Dependent Structural Plasticity and Associated Neurological Disorders

Neurodevelopmental disorders like autism spectrum disorder (ASD), fragile-X syndrome, and Rett's syndrome are associated with altered spine morphology and dendritic spine density (Nakai et al., 2018). Experimental studies suggest a relationship between dendritic defects and neurological disorders (Blanco-Suárez et al., 2017; Kim et al., 2017; Pyronneau et al., 2017; Baglietto-Vargas et al., 2018). Studies have found a link between intellectual disabilities and immature morphology of spines on cortical neurons (Martínez-Cerdeño, 2017; Nakao et al., 2017). Moreover, individuals with intellectual disabilities form fewer spines per dendritic branch (Martínez-Cerdeño, 2017). Several studies on cortical pyramidal neurons in the brain tissues of individuals with intellectual disabilities have confirmed the complexity reduction of both apical and basal dendrites (Kaufmann and Moser, 2000).

ASD is a group of complex neurodevelopment disorders characterized by distinctive and repetitive displays of problematic behavior and difficulties with social interaction and communication (Miranda et al., 2018). As the symptoms appear in early childhood, they have a long-lasting and ongoing effect on an individual's daily life. Histopathological studies have confirmed the presence of higher spine densities on the apical dendrites of layer II pyramidal neurons in the parietal, frontal and temporal lobes and the layer V projection neurons of the temporal lobe in individuals with ASD than in control subjects (Tang et al., 2014). This finding confirms that the balance between spine formation and elimination is disturbed. Similarly, MRI studies have confirmed an enlargement of gray matter and overall brain volume in individuals with ASD that usually appears before two years of age (Schumann et al., 2010; Hazlett et al., 2017). This period matches the dendritic development and rapid spine enlargement in the human brain that increases to the highest level in the first two years of life (Petanjek et al., 2011). ASD is characterized by overabundant spine growth during this period.

Alzheimer's disease (AD) is a neurodegenerative disease associated with a substantial loss of synapses and an overall reduction in synaptic density (DeKosky and Scheff, 1990; Forner et al., 2017). Post-mortem studies have confirmed that individuals with early-stage AD have significantly reduced synaptic density in the inferior temporal gyrus, which affects their verbal fluency (Scheff et al., 2011). In the CA1 region, the dentate gyrus, and in the posterior cingulate gyrus, which is a cortical region affected soon after the onset of AD (Scheff et al., 2015). Likewise, a recent experimental study revealed that progressive alteration of the dendritic spine causes the intraneuronal tau to aggregate (Merino-Serrais et al., 2013). In early AD, individuals display signs of mild cognitive loss; this occurs well in advance of large-scale synaptic impairment and neurodegeneration due to the accumulation of non-fibrillar, oligomeric amyloid β -peptides (A β). Soluble A β oligomers can adversely affect structural plasticity at deficient concentrations; the molecular substrates by which synaptic memory mechanisms are interrupted are not yet known (Skaper et al., 2017). In the mammalian central nervous system, the dendritic spine establishes a primary locus of excitatory synaptic transmission. In response to changes in hormonal status, developmental stage, and changes in afferent input, these structures, distending from dendritic shafts, suffer dynamic alterations in size, number and shape. It is perhaps not surprising that loss of spine density may be associated with cognitive impairment and memory loss in AD, even though the underlying mechanism(s) remain unclear (Skaper et al., 2017).

In schizophrenia, abnormal spine density has been reported in

multiple regions of the brain. The most convincing observation is a decrease in spine density on layer III pyramidal neurons of the neocortex in schizophrenic individuals compared to control subjects (Glantz and Lewis, 2000). A recent study reports a significant decrease in the number of small spines in pyramidal neurons present in the same layer of the auditory cortex (MacDonald et al., 2017). Likewise, post-mortem studies of schizophrenia have provided evidence for reduced basal dendritic density in the prefrontal cortex (layer III and layer V pyramidal neurons) compared to controls (Broadbelt et al., 2002).

Concluding Remarks and Future Directions

In this review, we have summarized some of the most recent advances in our understanding of how postsynaptic kinases and phosphatases signalling balance is essential for structural plasticity regulation at multiple levels. Dysregulation, or imbalance between these two key pathways, can have detrimental effects on the brain's cognitive functions. Future studies are needed to elucidate the relationship between activity-dependent regulation of these key molecules with morphological and structural changes in the brain. The advancement of new super-resolution microscopy methods allows for more detailed investigations of morphological changes in the synapse. Given that many neurological and neuropsychiatric disorders are explained by changes in synaptic plasticity, a clear insight of how kinases/phosphatase signalling pathways are organized at synapses will enable the development of new therapies and drugs designed to treat these diseases. Scaffolding interaction and targeting specific synapses could have many advantages, in terms of improved specificity and efficacy, over phosphatase catalytic and globally inhibiting kinase activity using existing pharmacological studies.

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